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Complications of spinal cord stimulation and peripheral nerve stimulation techniques: A review of the literature

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Running title: Complications of neurostimulation techniques: a review

ABSTRACT

Objective: Spinal cord and peripheral neurostimulation techniques have been practiced since 1967 for the relief of pain and some techniques are also used for improvement in organ function. Neuromodulation has recognised complications, although very rarely do these cause long term morbidity. The aim of this article is to present a review of complications observed in patients treated with neurostimulation techniques.

Methods: A review of the major recent publications in the literature on the subjects of spinal cord, occipital, sacral and peripheral nerve field stimulation was conducted.

Results: The incidence of complications reported varies from 30% to 40% of patients affected by one or more complications. Adverse events can be subdivided into hardware related complications and biological complications. The commonest hardware related complication is lead migration. Other lead related complications such as failure or fracture have also been reported. Common biological complications include infection and pain over the implant. Serious biological complications such as dural puncture headache and neurological damage are rarely observed.

Conclusions: Spinal cord and peripheral neurostimulation techniques are safe and reversible therapies. Hardware related complications are more commonly observed than biological complications. Serious adverse events such as neurological damage are rare.

INTRODUCTION

The electrical stimulation of the dorsal columns of the spinal cord to induce pain relief was first used in humans in 1967 [1]. Despite incomplete understanding of the mechanism of action, spinal cord stimulation (SCS) has become increasingly popular and its efficacy has been documented in neuropathic pain (level B) [2] as well as ischemic pain, whether due to peripheral vascular [3] or coronary artery disease [4]. Studies of SCS have shown that the therapy significantly improves the health related quality of life (HRQoL) of users [5].

A health economic assessment of SCS for the management of chronic neuropathic pain has shown the therapy to be cost-effective [6]. The Incremental Cost Effectiveness Ratio (ICER) calculated over a 15 years horizon was below £20,000 per quality adjusted life year (QALY) [6]. The cost of complications, which is included in the cost of the therapy, has been derived from the patient cohort of the PROCESS study and is estimated at an average of £576 per patient (SD of £1320) [7].

The complications of SCS are numerous and incidences of 30% to 40% have been reported in multiple studies [8-10]. Hardware-related problems such as lead failure and migration are more common than biological complications such as infection, pain, and wound breakdown [11, 12]. Infection is one of the major complications of SCS with incidences of 3.4% to 10%, and is a common cause for removal of the device and failure of therapy [13, 14]. A review has recommended an 18% budgetary allocation average per patient per annum for the maintenance of the therapy including complication management [13]. It is important to note that in device based therapies, the experience of the implanter impacts significantly on the rate of complications. This has been successfully demonstrated in the case of cardioverter defibrillator and total hip replacement [15].

The UK National Institute for Health and Care Excellence conclude in their Health Technology Appraisal of the therapy that among a total of 403 implanted patients across all trials examined, four (1%) device removals were required as a result of infection [16]. Across trials, the percentage of implantations requiring surgery to resolve a device-related complication, including device removals, ranged from 0% to 38%, which may be due to differences in follow- up periods, populations or clinical settings.

The aim of this review of the literature is to describe the rates of complications observed in spinal cord stimulation (SCS), occipital nerve stimulation (ONS), sacral nerve stimulation (SNS) and peripheral nerve field stimulation (PNFS).

METHODS

A review of studies that reported complications associated with the use of SCS, ONS, SNS and PNFS was conducted. We searched PubMed, Embase, Cochrane Library and Scopus up to December 2014. A combination of MeSH/Thesaurus terms and free-text terms was employed, including spinal cord stimulation, occipital nerve stimulation, sacral nerve stimulation, peripheral nerve field stimulation, complications, adverse events and side effects. The search was restricted to articles published in English. A hand-search of the reference lists of studies meeting the inclusion criteria was also performed.

Complications were stratified into the following categories:

1. Hardware related complications: the commonest being lead related complications such as lead migration or fracture, extension related complication, disconnection or misconnection and Implantable Pulse Generator (IPG) related complications such a battery depletion, flipping and recharging difficulties.

2. Biological complications: the commonest of which were infections, deep and superficial, the development of haematoma or seroma over the device or more commonly pain over the implanted hardware. Less frequent biological complications include dural puncture related headaches and the more serious nerve damage including spinal cord injury and paralysis [17].

3. Programming or therapy related complications: including loss of paraesthesia and painful or unpleasant paraesthesia. These are less threatening and can usually be addressed through programming, although on rare occasions can result in device removal due to therapy failure.

HARDWARE RELATED COMPLICATIONS

Lead Migration

Lead migration is by far the commonest complication of spinal and peripheral nerve stimulation. Peripheral lead migrations have been reported at rates as high as 100% in a case series of ONS at 3 years and 60% at the end of 1 year [18] and in 12 of 51 subjects (24%) in the ONSTIM study of ONS [19]. In both ONS studies, the leads were secured to fascia and positioned at the C1 level. In the ONSTIM study the lead extension was placed with circular coils, creating strain-relief loops but this was not employed consistently. The authors recommended the use of a strain-relief loop and preference for abdominal to buttock IPG positioning to study implanters when a number of lead migrations were reported.

For mainstream SCS in the hands of experienced implanters a lower incidence is accepted as standard. In SCS, the leads are placed in the epidural space in the spine near the region that supplies nerves to the painful area. Most reviews do not differentiate between vertical (cranio-caudal) and lateral (horizontal) lead migration. In a 20-year literature review of the therapy Cameron reported 361 lead migrations in 2753 patients giving an overall rate of 13.2% [20]. For the studies included in the review, the leads had been positioned either at the thoracic or cervical level, but it is not clear if there were differences in the lead migration

rates based on lead positioning. In an assessment of 18 studies of SCS in failed back surgery syndrome (FBSS) and 8 studies of SCS use in complex regional pain syndrome (CRPS) Taylor and colleagues report 20% and 27% respectively in lead related complications [21, 22]. No breakdown is described of the incidence of fracture and migration. In a review of 410 patients over a 22-year period Kumar et al report lead migrations in 88 patients (21.4%) of which 40 were repositioned and 48 were replaced [23]. The displacement of leads was twice higher in the cervical region as compared with lower dorsal placements with the authors considering this to be due to mobility of the cervical spine. In a more recent retrospective review of 707 patients with a mean follow-up of 3 years and 5 months (range: 3 months to 7 years), Mekhail et al report an initial lead migration rate of 0.7% during the trial period but a subsequent 119 cases of 527 (22.6%) developing lead migration [13]. The authors do not elaborate on the numbers of patients requiring revisions. Turner et al reviewed 22 studies of SCS; they did not report a rate of lead migration but instead reported a 23.1% rate of stimulator revision for reasons other than battery change with a median value of 21.5% and a range of 0-80% [11]. In their discussion the authors acknowledge that the majority of these occurrences would be related to lead migration, however it is not possible to estimate how many of these events were related to lead malfunction instead of migration. In the PROCESS study, at 24 months 9 events of lead migrations had occurred in 6 out of 42 patients (14%) with all six patients requiring surgery to reposition the leads [24]. In an earlier randomised controlled trial (RCT) comparing SCS to reoperation, North and co-authors report that 3/33 (9%) of patients required lead revision due to migration or malposition [25]. It is important to note that the patients in this study received mostly surgical plate leads. These are known to be associated with lower migration rates compared to the more commonly used cylindrical percutaneous leads [26, 27]. Two RCT's have recently evaluated SCS in patients with painful diabetic neuropathy (DN) [28, 29]. In both studies, the leads were positioned at the thoracic

level and anchored to the fascia. Lead migration was observed in one patient (2.5%) in the de Vos et al study [28]. It is not clear if lead migration was observed in the Slangen et al trial as only two serious adverse events were reported [29]. The authors mention that the complication rate in this study was comparable to that reported in the literature.

For sacral nerve stimulation, the electrode tip is placed near the sacral nerve. In a review of 7 RCTs and 47 case reports for SNS therapy in functional urinary bladder stimulation, Brazzelli et al conclude that lead migration in this therapy occurs in 16% of patients despite the use of tined leads [30].

For PNFS the leads are placed next to one of the peripheral nerves. In the largest case series reporting on the use of PNFS for pain relief, Sator-Katzenschlager [31] and Verrills [32] report rates of lead migration of 13% and 2% respectively. The leads were sutured to the deep fascia but from the studies, it is unclear the level at which the leads were placed. The large difference between both studies may well relate to the multicentre nature of the first study compared to the second, which reports a single centre practice and a different definition of migration. Indeed when a clinically significant definition of lead migration was adopted, only three of 143 patients (2.1%) required surgical revision [33]. This latest SCS retrospective review may well reflect improvement in anchoring technology over the last decade.

In conclusion lead migration remains the most common complication of spinal and peripheral nerve stimulation. Although paraesthesia coverage loss due to lead migration can be recaptured by reprogramming, the majority of the instances of major lead migration require minor reoperation to relocate the lead to its original position and most will incur the cost of a new lead [34]. Lead migration rates vary greatly between studies, with some quoting figures as high as 60-100%, but the majority quoting figures of 10-25% for spinal cord stimulation. This discrepancy can be explained by varying implanter experience, different definitions of “migration”, differing clinical context of the therapy, and differing clinical practices. Lead

migrations following surgical paddle lead implantation is less common than with percutaneous cylindrical leads and that location of the lead in the spine may influence the rate of migration, with higher rates occurring where the lead is implanted in a highly mobile area of the spine [34]. The impact of the recent improvements in hardware design on the incidence of lead migration remains unclear. Table 1 summarises the lead migration incidence quoted by various studies.

Table 1. Lead migration rates for SCS, SNS, ONS and PNFS

Publication	Therapy type	N	Migration rate %	Publication Type
Cameron 2004 [20]	SCS	2753	13.2%	Review article
Turner 2004 [35]	SCS	830	23.1%	Systematic review
North 2005 [25]	SCS	45	9%	RCT
Taylor 2005 [22]	SCS	112	27%	Systematic review
Taylor 2006 [21]	SCS	66	20%	Systematic review
Kumar 2006 [23]	SCS	410	21.4%	Retrospective Analysis
Kumar 2008 [24]	SCS	42	14%	RCT
Mekhail 2011 [13]	SCS	527	22.6%	Retrospective Analysis
Gazelka 2014 [33]	SCS	143	2.1%	Retrospective Review
de Vos 2014 [28]	SCS	40	2.5%	RCT
Total	SCS	4968	Range 2.1-27% Mean 15.49% 95% CI 9.21-21.77%	
Brazzelli 2006 [30]	SNS	785	16%	Systematic review
Schwedt 2007 [18]	ONS	15	60-100%	Retrospective Analysis
Paemeleire 2010 [36]	ONS	44	30%	Retrospective Analysis
Saper 2011 [19]	ONS	51	24%	RCT
Sator-Katzenschlager 2010 [31]	PNFS	111	13%	Retrospective Analysis
Verrills 2011 [32]	PNFS	100	2%	Retrospective Analysis

Confidence intervals are calculated at 95% level

Lead fracture and malfunction

Most studies report rates for either lead fracture, malfunction or general hardware malfunction. In the PROCESS study the rates are reported as lead or extension fractures, however the latter are very rare [24]. A total of 4 events in 3 out of 42 patients (7%) with only 1 requiring a surgical revision (2%) were observed [24]. A review identified 250 cases of lead breakage out of 2753 cases, an incidence of 9.1% [20]. In his review of 707 cases Mekhail and colleagues report lead connection failure occurring in 50 cases (9.5%) and lead breakage in 33 cases (6%) [13]. Kumar et al report 24 fractured electrodes out of 410 cases (5.9%) all of which were replaced satisfactorily [23]. The usual site of fracture was distal to the fixation point to the deep fascia where the lead enters the spinal canal [23]. Turner et al report on 20 studies of SCS with a mean incidence of equipment failure across studies of 10.2% and a median figure of 6.5% and a range of 0-40% [35]. No events related with lead fracture or malfunctions were reported in the de Vos RCT of SCS in diabetic neuropathy [28] while it was unclear if these events occurred in the Slangen et al study [29]. Paemeleire et al report on 44 patients implanted with ONS [36]. The authors note that revision was needed in about 30% of patients because of technical problems, which included lead fracture, dislocation and connector current leakage. Saper et al report one case of lead fracture at the C1 level in 51 cases in the ONSTIM study (2%) [19]. Brazzelli and co-authors report no cases of lead fracture in their review of SNS [30]. Table 2 summarises the incidence of lead migration in various studies of neuromodulation techniques.

Table 2. Lead fracture and malfunction rates for SCS, ONS and PNFS

Publication	Therapy type	N	Fracture rate %	Publication Type
Cameron 2004 [20]	SCS	2753	9.1%	Review article
Turner 2004 [35]	SCS	830	10.2%	Systematic review
Kumar 2006 [23]	SCS	410	5.9%	Retrospective Analysis
Kumar 2008 [24]	SCS	42	7%	RCT
Mekhail 2011 [13]	SCS	527	6%	Retrospective Analysis
de Vos 2014 [28]	SCS	40	0%	RCT
Total	SCS	4602	Range 0-10.2% Mean 6.37% 95% CI 2.63-10.10%	
Schwedt 2007 [18]	ONS	15	0%	Retrospective Analysis
Saper 2011 [19]	ONS	51	2%	RCT
Sator-Katzenschlager 2010 [31]	PNFS	111	5%	Retrospective Analysis
Verrills 2011 [32]	PNFS	100	2%	Retrospective Analysis

Confidence intervals are calculated at 95% level

Battery failure

The battery of an IPG is located within the device, when it is depleted, replacement requires repeated operation. When a battery requires replacement before the expected date (determined by the parameters being used by the patient), it is considered a battery failure. Battery failure occurred in 32 (1.7%) of 1900 cases examined by Cameron, although in 22 of 32 cases battery failure occurred after more than 3 years [20]. Turner et al reported much higher equipment failure rates of 10.2%, however this figure did not relate to battery failure

specifically but included all hardware failure [35]. Neither the Mekhail et al nor Kumar et al studies report on premature battery failure [13, 23]. No premature battery failures were reported as part of the PROCESS, North et al, de Vos et al or Slangen et al studies [24, 25, 28, 29]. No reports of battery replacement are available for ONS or SNS.

Premature battery depletion is a rare occurrence and shorter than expected lifespan have mostly non-technical causes, particularly when the manufacturer's instructions are properly followed. The current consumption depends on physiological factors (distance to the spinal cord), anatomical location (stimulation intensity usually smaller in the cervical region) and technical aspects such as the number of active contacts (increased current drain), the current intensity and the stimulation patterns. The latter has become a serious clinical concern as the new stimulation modes (high density, burst, high frequency) all have requirements that are several orders of magnitude higher than conventional stimulation. In concrete terms, the new modes of stimulation cannot be provided without batteries that can be recharged, and will have to do so every day in most cases.

Rechargeable batteries have been available for a relatively short time and the experience with these devices is limited both by the duration use and the paucity of the data available. Rechargeable IPG's have limited lifespans that can vary with manufacturers, but are usually 9 years or more. Though potentially more effective and versatile, rechargeable batteries require a higher level of patient understanding and awareness. Some of the early devices could not recover after extended period of depletion, a problem that has been largely addressed and solved in the newer generation. Though most depleted rechargeable generators can now be revived, the rebooting procedures may need the help of a trained technician. Recharging capabilities, which was initially perceived as a clinical advantage, has not always lived up to patient's expectations as the inconvenience of recharging has turned out to be a burden rather than a facility with some patients. From the cost

effectiveness standpoint, clinical as well as modelling studies have suggested that the implantation of a rechargeable system is indicated mainly when a cell-driven device last for less than approximately 4 years (6; 37). Theoretically, as the need for battery change is decreased, the number of surgical complications of these procedures should be minimised. To the best of our knowledge however there is currently no data and we can only speculate.

Another potentially unpleasant effect of recharging the battery is a heating sensation that is felt over the stimulation during the process. In the more extreme (and rare) cases recharging has to be made in multiple sequences in order to avoid excessive discomfort.

BIOLOGICAL COMPLICATIONS

Pain related to device components

Patients implanted with neuromodulation devices often report pains related to the site of device components such as pain around the IPG site or over the lead anchor site or lead extension junctions. In SCS studies the incidence is variable, for example Kumar et al report an incidence of 12% (5 of 42 patients) in the PROCESS study with one patient requiring reoperation [24]. This high incidence may however relate to the large size IPG used in the study - Synergy™ (Medtronic MN, USA). Kumar et al, observed an incidence of discomfort over the IPG of 1.2% (5/410) [23]. The RCT by North did not report on device related discomfort [25]. Two patients (5%) experienced pain over the IPG in the RCT by de Vos et al [28]. It is unclear if this was observed in the Slangen et al RCT [29]. Mekhail et al reported pain at the generator site in 86 (12%) of 707 patients [13]. Cameron reports 24 cases of device related discomfort out of a total of 2753 (0.9%) [20]. Turner and co-authors found a higher incidence with a mean of 5.8% of patients across 20 studies reporting pain over the implant with a median value of 0% and a range of 0-40% [35]. In ONS, Saper et al report 2 cases of pain over the IPG site and one case of burning pain over lead/extension site; a total

of 6% [19]. By contrast Paemeleire reports no cases of pain over the implant site [36]. This complication appears to be far more common in SNS. Brazzelli and collegues report a 25% incidence of pain over the lead or IPG site [30]. This may well relate to the location of the lead and IPG implant in the presacral and buttock area where subcutaneous fat may be denser than in the anterior abdominal wall, where most SCS devices are implanted. Pain at the IPG site according to where it was positioned is not commonly reported and it is not possible to determine if some implant sites are associated with more pain than others, however the IPG site selection may significantly influence patient satisfaction due to pain in the IPG site. Table 3 summarises the rates of implant-related pain observed.

Table 3. Rates of implant related pain for SCS, SNS and ONS

Publication	Therapy type	N	Pain over Implant %	Publication Type
Cameron 2004 [20]	SCS	2753	0.9%	Review article
Turner 2004 [35]	SCS	830	5.8%	Systematic review
Kumar 2006 [23]	SCS	410	1.2%	Retrospective Analysis
Kumar 2008 [24]	SCS	42	12%	RCT
Mekhail 2011 [13]	SCS	707	12%	Retrospective Analysis
de Vos 2014 [28]	SCS	40	5%	RCT
Total	SCS	4782	Range 0.9-12% Mean 6.15% 95% CI 0.97-11.33%	
Brazzelli 2006 [30]	SNS	653	25%	Systematic review
Saper 2011 [19]	ONS	51	6%	RCT

Confidence intervals are calculated at 95% level

Wound Infection (Superficial and Deep) and wound breakdown

Infection is one of the major complications of SCS, with incidences of 4% to 10%, and is a common cause for explantation of the device. This incidence is higher than the 2% to 5% rate associated with any surgery in the USA [13]. Kumar et al report 14 (3.4%) patients experienced infection, 4 of which resolved with antibiotics, whereas the other 10 required removal of the hardware and subsequent reinstallation [23]. In the PROCESS study 4/42 (10%) patients suffered wound infections, with two of those patients requiring surgery [24]. Mekhail et al report a total of 32 (4.5%) patients with documented infections, of which 22 cases had deep infections (20 had IPG pocket infections and 2 had lead track infections) [13]. The remaining 10 cases had superficial infections limited to the skin and subcutaneous tissues at the site of electrode entry over the spine. None of the patients with superficial infections had abscess, while 18 of the patients with deep tissue infections had documented abscesses. There was only 1 case of epidural infection without any evidence of abscess. This case was confirmed by a positive culture that was obtained during explantation surgery, from the epidural area. No infections were documented in any of the 707 SCS trials. No statistically significant difference was discovered between the various indications of SCS (rates varying from 0-6.3%) neither was there a significant difference in infection rates between diabetics and non-diabetics [13]. In contrast, relatively low incidences of infection in patients with peripheral vascular disease and visceral pain were observed. North and colleagues report two cases of infection (6%) one requiring device removal with the other treated with antibiotics [25]. Turner et al observed rates of superficial and deep infections averaging 4.5% and 0.1% respectively with median values of 4% and 0% and ranges of 0-12% and 0-1% [35]. Cameron reports 100 infections in 2972 implants a rate of 3.4% [20]. In a recent series of 53 SCS systems implanted in predominantly cancer patients the infection rate was 3.4% and was not

higher in cancer than non-cancer patients [38]. One infection during trial stimulation was observed in the de Vos SCS RCT for diabetic neuropathy [28]. This infection was resolved and followed by a permanent SCS implant. In the other RCT for SCS in diabetic neuropathy one patient contracted an infection of the SCS system six weeks post implantation requiring antibiotic treatment and system removal [29]. In ONS trials similar rates are described by Saper et al (4%) and Paemeleire et al (4.5%) [19, 36]. In SNS, Brazzelli and colleagues found wound problem rates of 7% and infection rates of 5% [30].

In a study reviewing 114 cases of infection Follett et al reported that 48% of the cases were due to *Staphylococcus* and 3% were due to *Pseudomonas* [39]. The remaining cases of infection were unknown/not reported (24%), showed no growth (18%), or were positive for multiple species (6%). Many studies have shown the generator pocket site to be the most common location of infection. Follett's review found 54% of the infections to be in the generator pocket. The SCS leads were infected 17% of the time, the lumbar incision site (8%), multiple sites (14%), and other/not reported (8%). Potential risk factors for infection or poor wound healing included diabetes, debilitated status, malnutrition, extremely thin body habitus, obesity, autoimmune disorder, corticosteroid use, decubitus ulcers, pre-existing infection, poor hygiene, urinary or faecal incontinence, and malabsorption syndrome [39].

The last resort treatment for an SCS infection is complete removal of the system and treatment with intravenous antibiotics. If the infection is confined to the generator site, one may only remove the generator and treat with antibiotics, leaving the leads in place. However, this may make it more difficult to eliminate the infection and often requires subsequent lead removal [39]. Eradication of infection without device removal or with partial device removal has been associated with lower success rates and higher relapse rates, which explains the high rates observed for total device explantation (82%) in comparison with partial device explantation (12%) and no explantation (4%) [39]. Both septic (MRSA) and

aseptic meningitis have been reported after SCS. There is a further case report of paralysis after epidural and intradural abscess formation at lead tip; despite lead explant and abscess excision the patient was left with an incomplete recovery [40].

Infection prevention techniques include administration of prophylactic antibiotics, adequate skin preparation, meticulous attention to sterile techniques in the operating room, and adequate wound haemostasis [39]. Table 4 summarises the rate of infection reported in the various studies.

Skin Erosion

Skin erosion of leads or hardware is an uncommon complication of spinal cord stimulation. Overall Cameron reports an incidence of skin erosion of 0.2% [20]. This is in contrast with subcutaneous nerve field stimulation where Verrills and colleagues report an incidence of 7% of hardware erosion in 100 cases [32].

Device Removal

There are many reasons for device removal including persistent or overwhelming infection, therapy failure, and persistent pain over hardware and skin erosion. Device removal is not reported in all SCS studies. Slangen et al report one patient (4.5%) that had the SCS system removed following infection [29]. The review by Turner et al report device removal incidence of 11% with a median figure of 6% and a range of 0-47%, although the authors do not elaborate on the causes for device removals [35]. Brazzelli et al note an incidence of 9% of device removal in SNS [30]. Verrills et al describe two cases (2%) of hardware failure and removal in PNFS [32].

Table 4. Rates of infection for SCS, SNS, ONS and PNFS

Publication	Therapy type	N	Infection %	Publication Type
Cameron 2004 [20]	SCS	2972	3.4%	Review article
Follett 2004 [38]	SCS	114	N/A	Retrospective review
Turner 2004 [35]	SCS	830	4.6%	Systematic review
North 2005 [25]	SCS	45	6%	RCT
Taylor 2005 [22]	SCS	112	6%	Systematic review
Taylor 2006 [21]	SCS	66	4%	Systematic review
Kumar 2006 [23]	SCS	410	3.4%	Retrospective Analysis
Kumar 2008 [24]	SCS	42	10%	RCT
Mekhail 2011 [13]	SCS	527	4.5%	Retrospective Analysis
de Vos 2014 [28]	SCS	40	2.5%	RCT
Slangen 2014 [29]	SCS	22	4.5%	RCT
Total	SCS	5180	Range 2.5-10% Mean 4.89% 95% CI 3.38-6.39%	
Brazzelli 2006 [30]	SNS	727	5%	Systematic review
Pameleire 2010 [36]	ONS	44	4.5%	Retrospective Analysis
Saper 2011 [19]	ONS	51	4%	RCT
Sator-Katzenschlager 2011 [31]	PNFS	111	6%	Retrospective Analysis
Verrills 2011 [32]	PNFS	100	1%	Retrospective Analysis

Confidence intervals are calculated at 95% level

Dural Puncture

Accidental dural puncture can occur during epidural needle placement in lead positioning. This can result in post-dural puncture headache symptoms as well as CSF leak into the wound. It has been suggested that risk factors for the development of a dural puncture include gender [11.1% female vs. 3.6% male, OR 2.25 (1.07-4.73); p = 0.03], age [11.0% 31-50 years

of age vs. 4.2% others, OR 2.21 (1.12-4.36); $p = 0.02$], previous history of post-dural puncture headache [26.4% positive vs. 6.2% negative, OR 4.30 (1.99-9.31); $p < 0.01$] and bevel orientation [16.1% perpendicular vs. 5.7% parallel, OR 2.16 (1.07-4.35); $p = 0.03$] [41]. The incidence of dural puncture has been estimated at 0-0.3% [12, 20]. Patients who experience post dural puncture headache may suffer from a positional headache, diplopia, tinnitus, neck pain, photophobia, and fluid accumulation at the lead anchoring site during the perioperative period. These patients will be unable to perform their activities of daily living and are therefore unable to assess the efficacy of an SCS trial [14]. The initial approach is to suggest bed rest but if the symptoms persist, the treatment options are either a blood patch or surgical exploration [14]. Epidural blood patch has been found to be an effective treatment for severe post-dural puncture headache, although its effectiveness is decreased if the dura mater puncture is caused by a large bore needle [42]. Surgical closure of the dural perforation is a last resort option for leaks that are unresponsive to other therapies [43].

Neurological Injury

Neurological injury is by far the most dreaded complication of SCS. This can result from direct trauma caused by needle puncture, percutaneous lead placement or during surgery for placement of paddle leads. Delayed neurological damage can result from epidural haematoma or abscess formation. Epidural haematoma formation following the placement of SCS leads is a rare occurrence and has been observed mainly following the insertion of paddle leads inserted via direct surgical access. One patient in the Slangen et al RCT developed postdural puncture headache following a dural puncture, which was complicated by a lethal subural hematoma 3 days after the procedure [29]. In a series of 509 plate electrodes Barolat reported 1 case of epidural haematoma resulting in paraplegia [17]. In a 20 year review of the literature Cameron estimated the risk of epidural haematoma development at 0.3% and

paralysis at 0.03% [20]. In a more recent attempt to review the literature for incidence of neurological damage following surgical paddle lead implantation, Levy and colleagues report 111 (0.25%) cases of major neurologic deficit in a sample of 44,587 cases, 61 (0.14%) limited motor deficit, 6 cases of autonomic changes (0.013%) 46 cases of sensory deficit (0.10%) as well as 21 cases of cerebrospinal fluid leakage due to dural puncture [40]. Sixteen epidural hematomas with limited motor deficit are reported in the same series as well as 52 epidural hematomas with major motor deficit (0.12%) and 15 epidural hematomas without motor deficit (0.034%). Early recognition and treatment of neurological deficit allows functional recovery in most cases [44]. Trials studying techniques such as SNS, ONS and PNFS have not reported complications related to neurological damage.

Many of the potential SCS patients are medicated with serotonin reuptake inhibitors, acetylsalicylic acid (aspirin), nonsteroidal anti-inflammatory drugs and anticoagulants, all of which may increase the risk of post-operative epidural hematomas. Recommendations for interventional spine and pain procedures in patients on antiplatelets/anticoagulants are now available and should be implemented according to the patient perioperative medication [45]. The application of these recommendations can lead to a decrease in the risk of epidural or spinal hematoma. Alcohol consumption greater than 10 units a week, multilevel procedure, and previous spinal surgery have also been identified as risk factors for developing spinal epidural hematoma [46].

FACTORS AFFECTING THE RATE OF OCCURRENCE OF COMPLICATIONS

A number of factors may affect the rate of occurrence of complications in peripheral neuromodulation techniques.

Location of the lead

A differential in the rate of occurrence of lead migration has been observed when the use of spinal cord stimulation was examined for differing indications. For example locating the lead in the relatively immobile thoracic spine for indications such as refractory angina was associated with lower lead migrations rates. In a review of the subject Taylor et al report a combined rate of lead migration or fracture of 7.8% (10 out of 128 patients) [4]. This is much lower than the rates the same author observed for CRPS (20%) and FBSS (27%) [21, 22]. We may conclude that the position of the lead in a non-mobile area of the spine has a limiting effect on the rate of migrations. However we must note that time since implant, anchoring technique and hardware improvements may act as confounding factors.

There is no study that compares different techniques of implantation and/or anchoring electrodes. Anchoring device preferences and techniques are based on personal experience or theoretical concepts that make intuitive sense, but have not been actually tested in vivo. What most implanters would agree with is that the provision of strain relief loops in electrodes as well as extensions seems to improve the stability of the stimulating portion of the electrode.

Epidural vs. extra-spinal position of the lead

While one would expect an epidural position of the lead to impart a stabilising effect on the lead used for SCS, the figures do not seem to support this conclusion. For example in the case of PNFS where rates of lead migration and fracture are lower than, or similar to, those reported for SCS in general. Sator-Katzenschlager et al report a lead migration rate of 13% for PNFS, and an overall rate of complications of 24% which is similar to SCS reported rates in general [31]. This contrasts with higher rates reported for techniques such as ONS where Paemeleire et al [36] reports 14/44 patients (31.8%) requiring lead replacement and Schwedt reported rates of lead migration of 24% within three months of stimulator implantation and

100% at 3-year follow-up [18, 47]. These rates do not take into consideration the experience of the operator performing the technique. Bias in reporting of complications in retrospective case series cannot be ruled out.

Relative novelty of a technique and operating surgeon's experience

Other implant disciplines have demonstrated a clear link between the level of experience of the operating surgeon and the rate of occurrence of complications related to the implant procedure [15, 48, 49]. This seems to be the case in the world of neuromodulation, where early work on ONS by Schwedt [18] was associated with a much higher rate of complications relative to the later reports by Paemeleire [36] and Saper [19].

In the field of spinal cord stimulation a recent cohort study by Turner et al utilised non-experienced implanters and consequently reported higher complication rates as well as the occurrence of rare life threatening complications [50]. Furthermore, early SCS work by Andersen [51] in SCS for refractory angina treatment reported an incidence of lead migration of 23% versus a more recently reported incidence of 7.8% by Taylor et al [5]. We can therefore suggest that novel techniques in spinal and peripheral nerve stimulation may be associated with a higher rate of complications, particularly lead related complications, and that as surgeons gain experience in a particular implant technique the complication rates reduce over time. This seems to be the case with SCS of the dorsal root ganglion, a newly developed technique for the management of chronic neuropathic pain. A recent report with 1-year follow-up of 32 patients in which this intervention was used, observed a higher overall incidence of adverse events when compared with SCS [52]. Forty-three adverse events considered by the authors not to be related with the SCS system were observed, of which the most common were CSF leak with associated headache (8.5%), and infection (8.5%). A field safety action notice has been issued by the manufacturer of SCS for DRG advising how to

remove a lead [53]. According to the manufacturer as of May 2014, over 2000 DRG leads had been implanted and there had been 10 reports of lead breakage during attempted lead removal which resulted in lead fragments.

In an initial feasibility study investigating stimulation of the multifidus muscle for the management of low back pain, 5 of the 26 implanted patients decided to withdraw from the study due to lead dislocation in the first 60 days of treatment [54]. The authors used SCS systems and leads from different manufacturers for this feasibility study. A new system and leads have now been developed purposefully for the stimulation of the multifidus muscle. Studies are ongoing to investigate this new technique for the management of low back pain.

Hardware appropriateness for the procedure

Hardware for peripheral and spinal cord stimulation techniques has evolved significantly over the last 4 decades. While we continue to await the introduction of custom made hardware for particular techniques such as ONS and PNFS, such custom made hardware is already in existence for SCS and SNS. In SCS the hardware has evolved from monopolar leads through quadripolar leads to the current state of the art 16 contact leads. Early reports of complications, particularly the need for lead replacement, show a statistically significant lower rate in patients with quadripolar leads (11%) than in those with monopolar electrodes (45%) ($p < 0.003$) [51]. As there was no difference in the frequency of electrode migration between the two types of electrodes, proper paraesthesia coverage was most often recaptured by reprogramming with the multipolar leads [51]. North et al reported SCS treatment in 62 patients with chronic pain [55]. They found that surgical revision was necessary in 23% of the cases in which simple bipolar leads were placed to obtain optimal paraesthesia coverage. Surgical revision, however, was required in only 16% of those cases with multichannel devices. The drive to increase the number of contacts on an electrode array is the idea that

reprogrammation can restore appropriate stimulation if the electrode migrates in a cranio-caudal direction. This is largely supported by common sense rather than by clinical studies. There is no credible data to suggest the rate of revision has been minimised by the increased number of contacts, though the speculations are convincing. In addition, it is generally believed that the reimbursement strategy (payment per contact) that prevailed in the USA for a number of years has strongly encouraged the production and the use of electrodes carrying an increasing number of contacts.

Finally the introduction of rechargeable pulse generators may well reduce the need for battery replacements in a population of neurostimulation patients, particularly those indications requiring high current consumption such as peripheral arterial disease [56]. However this fact remains to be established in the long term.

Reporting of Complications

The reporting of incidences of complications in neuromodulation studies remains variable. This relates to the varying denominator in the formula used for percentage incidence calculations. While the majority of studies report the incidence of complications in percentage some studies consider the total number of subjects included in the study [54, 57] as the denominator while other consider the subjects trialled, implanted or in some cases the total number of adverse events [58] has been used to express an incidence of adverse events.

A more helpful format for the reader would be to report adverse events and complications in a table format showing the type and adverse events and the number of occurrences in the study as well as number of patients affected by the event. This would be followed by a percentage expressing a clear denominator /N figure on the table. While dividing by the number of subjects intended to receive the therapy seems at first glance the most appropriate

way forward, one needs to consider that some adverse events are inapplicable to some of the subjects, such as pocket pain, which is unlikely in subjects who have had a failed trial.

In the United States, the American Society of Anesthesiologists Closed Claims Project database collets malpractice insurance organisation claim files. The database consists of standardised summaries of each case and includes a detailed narrative summary of each claim. This database allows identification of major safety concerns, patterns of injury and strategies for prevention to improve patient safety by anaesthesiologists and may provide further data to that available in the current literature.

CONCLUSION

Spinal cord and peripheral nerve stimulation therapies are safe and reversible therapies. These effective therapeutic techniques may result in a range of minor complications. Hardware related complications are more common than biological complications with lead related complications most frequent. Biological complications include commoner complications such as infection and pain over the implant. Serious adverse events such as neurological damage are uncommon.

The rate of development of complications is governed by factors such as the lead position in the spine or periphery, the experience of the surgeon and the availability of custom made equipment for the technique.

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REFERENCES

1. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. Anesth Analg 1967;46(4):489-91.

2. Cruccu G, Aziz TZ, Garcia-Larrea L, Hansson P, Jensen TS, Lefaucheur JP, Simpson BA, Taylor RS. EFNS guidelines on neurostimulation therapy for neuropathic pain. Eur J Neurol 2007;14(9):952-70.

3. Ubbink DT, Vermeulen H. Spinal cord stimulation for critical leg ischemia: a review of effectiveness and optimal patient selection. J Pain Symptom Manage 2006;31(4 Suppl):S30-5.

4. Taylor RS, De Vries J, Buchser E, Dejongste MJ. Spinal cord stimulation in the treatment of refractory angina: systematic review and meta-analysis of randomised controlled trials. BMC Cardiovasc Disord 2009;9:13.

5. Eldabe S, Kumar K, Buchser E, Taylor RS. An analysis of the components of pain, function, and health-related quality of life in patients with failed back surgery syndrome treated with spinal cord stimulation or conventional medical management. Neuromodulation 2010;13(3):201-9.

6. Taylor RS, Ryan J, O'Donnell R, Eldabe S, Kumar K, North RB. The cost-effectiveness of spinal cord stimulation in the treatment of failed back surgery syndrome. Clin J Pain 2010;26(6):463-9.

7. Manca A, Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, Taylor RJ, Goeree R, Sculpher MJ. Quality of life, resource consumption and costs of spinal cord stimulation versus conventional medical management in neuropathic pain patients with failed back surgery syndrome (PROCESS trial). Eur J Pain 2008;12(8):1047-58.

8. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. Pain 2007;132(1-2):179-88.

9. Kemler MA, Barendse GA, van Kleef M, de Vet HC, Rijks CP, Furnée CA, van den Wildenberg FA. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. N Engl J Med 2000;343(9):618-24.

10. Kumar K, North R, Taylor R, Sculpher M, Van den Abeele C, Gehring M, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Fortini G, Richardson J, Buchser E, Tracey S, Reny P, Brookes M, Sabene S, Cano P, Banks C, Pengelly L, Adler R, Leruth S, Kelly C, Jacobs M. Spinal Cord Stimulation vs. Conventional Medical Management: A Prospective, Randomized, Controlled, Multicenter Study of Patients with Failed Back Surgery Syndrome (PROCESS Study). Neuromodulation 2005;8(4):213-8.

11. Turner JA, Loeser JD, Bell KG. Spinal cord stimulation for chronic low back pain: a systematic literature synthesis. Neurosurgery 1995;37(6):1088-95.

12. Kumar K, Wilson JR, Taylor RS, Gupta S. Complications of spinal cord stimulation, suggestions to improve outcome, and financial impact. J Neurosurg Spine 2006;5(3):191-203.

13. Mekhail NA, Mathews M, Nageeb F, Guirguis M, Mekhail MN, Cheng J. Retrospective review of 707 cases of spinal cord stimulation: indications and complications. Pain Pract 2011;11(2):148-53.

14. Woods DM, Hayek SM, Bedder M. Complications of neurostimulation. Techniques in Regional Anesthesia & Pain Management 2007;11(3):178-82.

15. Katz JN, Phillips CB, Baron JA, Fossel AH, Mahomed NN, Barrett J, Lingard EA, Harris WH, Poss R, Lew RA, Guadagnoli E, Wright EA, Losina E. Association of hospital and surgeon volume of total hip replacement with functional status and satisfaction three years following surgery. Arthritis Rheum 2003;48(2):560-8.

16. Simpson EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. Health Technol Assess 2009;13(17): 1-154.

17. Barolat G. Experience with 509 plate electrodes implanted epidurally from C1 to L1. Stereotact Funct Neurosurg 1993;61(2):60-79.

18. Schwedt TJ, Dodick DW, Hentz J, Trentman TL, Zimmerman RS. Occipital nerve stimulation for chronic headache--long-term safety and efficacy. Cephalalgia 2007;27(2):153-7.

19. Saper JR, Dodick DW, Silberstein SD, McCarville S, Sun M, Goadsby PJ; ONSTIM Investigators. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. Cephalalgia 2011;31(3):271-85.

20. Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. J Neurosurg 2004;100(3 Suppl Spine):254-67.

21. Taylor RS, Van Buyten JP, Buchser E. Spinal cord stimulation for complex regional pain syndrome: a systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. Eur J Pain 2006;10(2):91-101.

22. Taylor RS, Van Buyten JP, Buchser E. Spinal cord stimulation for chronic back and leg pain and failed back surgery syndrome: a systematic review and analysis of prognostic factors. Spine 2005;30(1):152-60.

23. Kumar K, Hunter G, Demeria D. Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience. Neurosurgery 2006;58(3):481-96.

24. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. Neurosurgery 2008;63(4):762-70.

25. North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial. Neurosurgery 2005;56(1):98-106.

26. North RB, Kidd DH, Olin J, Sieracki JN, Petrucci L. Spinal cord stimulation for axial low back pain: A prospective controlled trial comparing 16-contact insulated electrodes with 4-contact percutaneous electrodes. Neuromodulation 2006;9(1):56-67.

27. North RB, Kidd DH, Olin J, Sieracki JM, Farrokhi F, Petrucci L, Cutchis PN. Spinal cord stimulation for axial low back pain: a prospective, controlled trial comparing dual with single percutaneous electrodes. Spine 2005;30(12):1412-8.

28. de Vos CC, Meier K, Zaalberg PB, Nijhuis HJ, Duyvendak W, Vesper J, Enggaard TP, Lenders MW. Spinal cord stimulation in patients with painful diabetic neuropathy: A multicentre randomized clinical trial. Pain 2014; 155(11):2426-31.

29. Slangen R, Schaper NC, Faber CG, Joosten EA, Dirksen CD, van Dongen RT, Kessels AG, van Kleef M. Spinal cord stimulation and pain relief in painful diabetic peripheral neuropathy: a prospective two-center randomized controlled trial. Diabetes Care 2014; 37(11): 3016-24.

30. Brazzelli M, Murray A, Fraser C. Efficacy and safety of sacral nerve stimulation for urinary urge incontinence: a systematic review. J Urol 2006;175(3 Pt 1):835-41.

31. Sator-Katzenschlager S, Fiala K, Kress HG, Kofler A, Neuhold J, Kloimstein H, Ilias W, Mozes-Balla EM, Pinter M, Loining N, Fuchs W, Heinze G, Likar R. Subcutaneous target stimulation (STS) in chronic noncancer pain: a nationwide retrospective study. Pain Pract 2010; 10(4): 279-86.

32. Verrills P, Vivian D, Mitchell B, Barnard A. Peripheral nerve field stimulation for chronic pain: 100 cases and review of the literature. Pain Med 2011; 12(9): 1395-405.

33. Gazelka HM, Freeman ED, Hooten WM, Eldrige JS, Hoelzer BC, Mauck WD, Moeschler SM, Pingree MJ, Rho RH, Lamer TJ. Incidence of Clinically Significant Percutaneous Spinal Cord Stimulator Lead Migration. Neuromodulation 2015;18(2):123-5.

34. Kumar K, Buchser E, Linderoth B, Meglio M, Van Buyten JP. Avoiding complications from spinal cord stimulation: Practical recommendations from an international panel of experts. Neuromodulation 2007;10(1):24-33.

35. Turner JA, Loeser JD, Deyo RA, Sanders SB. Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications. *Pain* 2004;108(1-2):137-47.

36. Paemeleire K, Van Buyten JP, Van Buynder M, Alicino D, Van Maele G, Smet I, Goadsby PJ. Phenotype of patients responsive to occipital nerve stimulation for refractory head pain. Cephalalgia 2010;30(6):662-73.

37. Taylor RJ, Taylor RS. Spinal cord stimulation for failed back surgery syndrome: a decision-analytic model and cost-effectiveness analysis. Int J Technol Assess Health Care 2005;21(3):351-8.

38. Engle MP, Vinh BP, Harun N, Koyyalagunta D. Infectious complications related to intrathecal drug delivery system and spinal cord stimulator system implantations at a comprehensive cancer pain center. Pain Physician 2013;16(3):251-7.

39. Follett KA, Boortz-Marx RL, Drake JM, DuPen S, Schneider SJ, Turner MS, Coffey RJ. Prevention and management of intrathecal drug delivery and spinal cord stimulation system infections. Anesthesiology 2004;100(6):1582-94.

40. Levy R, Henderson J, Slavin K, Simpson BA, Barolat G, Shipley J, North R. Incidence and avoidance of neurologic complications with paddle type spinal cord stimulation leads. Neuromodulation 2011;14(5):412-22.

41. Amorim JA, Gomes de Barros MV, Valença MM. Post-dural (post-lumbar) puncture headache: risk factors and clinical features. Cephalalgia 2012;32(12):916-23.

42. Safa-Tisseront V, Thormann F, Malassiné P, Henry M, Riou B, Coriat P, Seebacher J. Effectiveness of epidural blood patch in the management of post-dural puncture headache. Anesthesiology 2001;95(2):334-9.

43. Turnbull DK, Shepherd DB. Post-dural puncture headache: pathogenesis, prevention and treatment. Br J Anaesth 2003;91(5):718-29.

44. Mammis A, Bonsignore C, Mogilner AY. (2013) Thoracic radiculopathy following spinal cord stimulator placement: case series. Neuromodulation 2013;16(5):443-8.

45. Narouze S, Benzon HT, Provenzano DA, Buvanendran A, De Andres J, Deer TR, Rauck R, Huntoon MA. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications: guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. Reg Anesth Pain Med 2015;40(3):182-212.

46. Amiri AR, Fouyas IP, Cro S, Casey AT. Postoperative spinal epidural hematoma (SEH): incidence, risk factors, onset, and management. Spine J 2013;13(2):134-40.

47. Schwedt TJ. Occipital nerve stimulation for chronic migraine--interpreting the ONSTIM feasibility trial. Cephalalgia 2011;31(3):262-3.

48. Losina E, Barrett J, Mahomed NN, Baron JA, Katz JN. Early failures of total hip replacement: effect of surgeon volume. Arthritis Rheum 2004;50(4):1338-43.

49. Al-Khatib SM, Lucas FL, Jollis JG, Malenka DJ, Wennberg DE. The relation between patients' outcomes and the volume of cardioverter-defibrillator implantation procedures performed by physicians treating Medicare beneficiaries. J Am Coll Cardiol 2005;46(8):1536-40.

50. Turner JA, Hollingworth W, Comstock BA, Deyo RA. Spinal cord stimulation for failed back surgery syndrome: outcomes in a workers' compensation setting. Pain 2010;148(1):14-25.

51. Andersen C. (1997) Complications in spinal cord stimulation for treatment of angina pectoris. Differences in unipolar and multipolar percutaneous inserted electrodes. Acta Cardiol 1997;52:325-33.

52. Liem L, Russo M, Huygen FJ, Van Buyten JP, Smet I, Verrills P, Cousins M, Brooker C, Levy R, Deer T, Kramer J. One-year outcomes of spinal cord stimulation of the dorsal root ganglion in the treatment of chronic neuropathic pain. Neuromodulation 2015;18(1):41-8.

53.http://www.mhra.gov.uk/home/groups/fsn/documents/fieldsafetynotice/con423469.pdf [Assessed 15th January 2015]

54. Van Buyten JP, Deckers, K, De Smedt K, Rens A, Smet I, Baranidharan G, Eldabe S, Gulve A, De Andres J, Gilligan C. A new therapy for patients with non-specific low

back pain: Results of a European multicenter feasibility study. Neuromodulation 2013;16: e176-7.

55. North RB, Ewend MG, Lawton MT, Piantadosi S. (1991) Spinal cord stimulation for chronic, intractable pain: superiority of "multi-channel" devices. Pain 1991;44(2):119-30.

56. Van Buyten JP. The performance and safety of an implantable spinal cord stimulation system in patients with chronic pain: A 5-year study. Neuromodulation 2003;6(2):79-87.

57. Al-Kaisy A, Van Buyten JP, Smet I, Palmisani S, Pang D, Smith T. Sustained effectiveness of 10 kHz high-frequency spinal cord stimulation for patients with chronic, low back pain: 24-month results of a prospective multicenter study. Pain Med 2014;15(3):347-54.

58. Liem L, Russo M, Huygen FJ, Van Buyten JP, Smet I, Verrills P, Cousins M, Brooker C, Levy R, Deer T, Kramer J. A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. Neuromodulation 2013;16(5):471-82.